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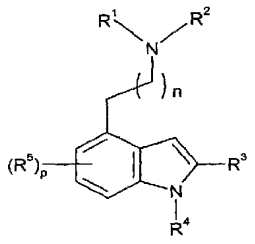
(54) Title: USE OF INDOLE AND INDOLINE DERIVATIVES IN THE TREATMENT OF OBESITY OR FOR THE REDUCTION OF FOOD INTAKE



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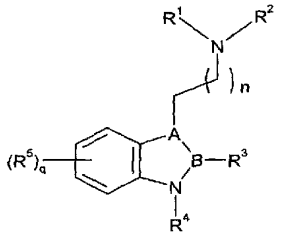

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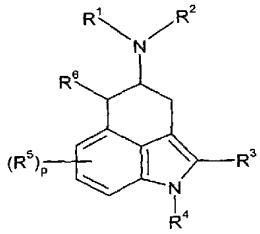

(III)

(57) Abstract: The invention provides the use of an indole or indoline derivative of Formula, II or III: wherein the substituents are as described in the specification; in the manufacture of a medicament for the treatment or prophylaxis of obesity or for the reduction of food intake. The invention also relates to the use of indole or indoline derivatives of Formula I, II or III for improving the bodily appearance of a mammal by causing loss of weight, as well as cosmetic compositions containing said compounds.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

USE OF INDOLE AND INDOLINE DERIVATIVES IN THE TREATMENT OF OBESITY OR FOR THE REDUCTION OF FOOD INTAKE

Technical Field

The present invention relates to the use of indole and indoline derivatives, which bind selectively to 5-HT_6 receptors, in the treatment of obesity or for the reduction of food intake.

Background Art

Obesity is a condition characterized in an increase in body fat content resulting in excess body weight above accepted norms. Obesity is the most important nutritional disorder in the western world and represents a major health problem in all industrialized countries. This disorder leads to increased mortality due to increased incidences of diseases such as cardiovascular disease, digestive disease, respiratory disease, cancer and NIDDM (type II diabetes). Searching for compounds which reduce body weight has been going on for many decades. One line of research has been activation of serotonergic systems, either by direct activation of serotonin receptor subtypes or by inhibiting serotonin re-uptake. The exact receptor subtype profile required is however not known.

Serotonin (5-hydroxytryptamine or 5-HT), a key transmitter of the peripheral and central nervous system, modulate a wide range of physiological and pathological functions, including anxiety, sleep regulation, aggression, feeding and depression. Multiple serotonin receptor subtypes have been identified and cloned. One of these, the 5-HT_6 receptor, was cloned by several groups in 1993 (Ruat et al. (1993) Biochem. Biophys. Res. Commun., 193: 268-276; Sebben et al. (1994) NeuroReport 5: 2553-2557) This receptor is positively coupled to adenylyl cyclase and displays affinity for antidepressants such as clozapine. Recently, the effect of 5-HT_6 antagonist and 5-HT_6 antisense oligonucleotides to reduce food intake in rats has been reported (Bentley et al. (1999) Br. J. Pharmac. Suppl 126: P66; Bentley et al. (1997) J. Psychopharmacol. Suppl. A64: 255; Woolley, M.L. et al. (2001) Neuropharmacology 41: 210-219).

U.S. patent No. 6,187,805 (see also Russell, M.G.N. et al. (2001) "N-Arylsulfonylindole Derivatives as Serotonin 5-HT_6 Receptor Ligands", J. Med. Chem. *in*

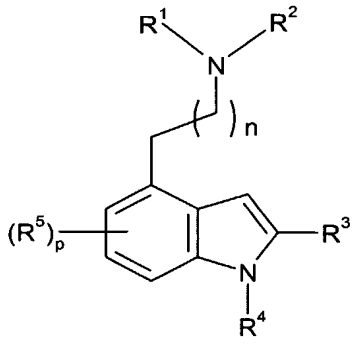
press) disclose indole and indoline derivatives as ligands selective for the 5-HT_6 receptors, and of proposed value in the treatment or prevention of CNS disorders, including Alzheimer's disease, Parkinson's disease, schizophrenia, depression and anxiety. However, such compounds have not been disclosed that such derivatives are useful for the treatment of obesity.

Brief description of the Drawings

Figure 1 is a graph depicting the effect on food intake in obese mice by administration of a compound according to the invention.

Disclosure of the Invention

It has been found that 5-HT_6 receptor antagonists, belonging to the class of indole or indoline derivatives disclosed in US 6,187,805, reduce food intake and body weight. Consequently, the present invention provides a method for the treatment or prophylaxis of obesity or for the reduction of food intake in mammals, including humans. The method comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I, II or III:



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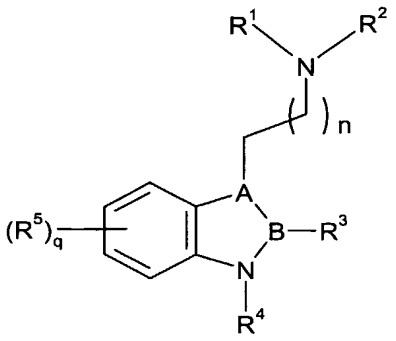

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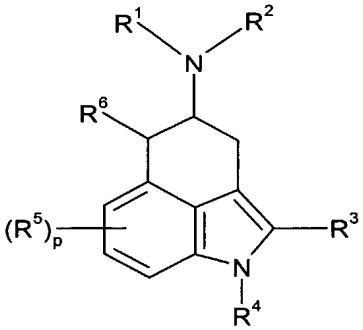


(III)

wherein

n is 1 or 2;

p is 0,1,2 or 3;

q is 0,1,2,3 or 4;

R^1 and R^2 independently represent hydrogen, C_{1-6} alkyl or aryl (C_{1-6})alkyl, or together represent the atoms necessary to complete a heterocycloalkyl group comprising the nitrogen atom to which R^1 and R^2 are attached;

R^3 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl(C_{1-6})alkyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, C_{1-6} alkylcarbonyl, or C_{1-6} alkoxycarbonyl;

R^4 represents arylsulphonyl, heteroarylsulphonyl, C_{1-6} alkylsulphonyl, di(C_{1-6})alkylaminosulphonyl, arylcarbonyl, C_{1-6} alkylcarbonyl, heteroarylcarbonyl or C_{1-6} alkoxycarbonyl;

each R^5 independently represents hydrogen, hydroxy, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy, nitrile or halogen;

R^6 represents hydrogen, hydroxy or C_{1-6} alkoxy; and

A–B represents C=C or CH–CH.

In Formulae I-III, one or more substituents may be present on any alkyl or aryl group represented by any of R^1 –R^5, or on any alkyl or aryl moiety of a group represented by any of R^1 –R^5. Preferred substituents include C_{1-6} alkyl, halogen, hydroxy and C_{1-6} alkoxy.

The expression "C_{1-6} alkyl" includes methyl and ethyl groups, and straight-chained, branched or cyclic propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and tert-butyl. Derived expressions such as "C_{1-6} alkoxy", "C_{1-6} alkylthio" and "C_{1-6} alkylamino" are to be construed accordingly.

The expression "C_{2-6} alkenyl" as used herein refers to straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl, allyl, dimethylallyl and butenyl groups.

The expression "C_{2-6} alkynyl" as used herein refers to straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

The term "aryl" refers to an aromatic ring system (monocyclic or bicyclic, only one ring need be aromatic) having from 6 to 10 ring carbon atoms. Typical aryl groups include phenyl and naphthyl.

The expression "aryl(C_{1-6})alkyl" as used herein includes benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl groups.

The term "heteroaryl" refers to an aromatic ring system (monocyclic or bicyclic, only one ring need be aromatic) having from 5 to 10 ring atoms, in which one or more of the rings atoms are heteroatoms, such as nitrogen, sulphur, and oxygen, and the remainder are carbon atoms. Suitable heteroaryl groups include pyridinyl, quinolinyl,

isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially chlorine or fluorine.

Further, the invention relates to the use of compounds of Formula I, II and II, as described herein, in the manufacture of a medicament for the treatment of obesity or for the reduction of food intake.

The invention also relates to the cosmetic use of compounds of Formula I, II and II, as described herein, for causing loss of weight, as well as cosmetic compositions containing said compounds. The invention further provides a non-therapeutic method of improving the bodily appearance of a mammal, including a human, which comprises orally administering to said mammal a compound of formula I, II or III as described herein.

For use in medicine, the salts of the compounds of Formulae I-III will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of Formulae I-III or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of Formulae I-III include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of Formulae I-III carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope the use of prodrugs of the compounds of Formulae I–III above. In general, such prodrugs will be functional derivatives of the compounds of Formulae I–III which are readily convertible *in vivo* into

the required compounds of Formulae I–III. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985.

Certain compounds according to the present invention may be capable of existing as tautomeric forms. It is to be understood that all possible tautomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

Where the compounds according to the invention have at least one asymmetric center, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

In Formulae I-III, suitable separate identities for R^1 and R^2 include hydrogen, methyl, ethyl, propyl and benzyl, and suitable identities for R^1 and R^2 in combination include pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl and morpholinyl.

Suitable identities for R^3 include hydrogen, methyl, ethyl, benzyl, allyl, propargyl, benzoyl, phenyl, thienyl, furoyl and ethoxycarbonyl.

Suitable identities for R^4 include benzenesulphonyl, 2-naphthalenesulphonyl, o-, m- or p-toluenesulphonyl, o-, m- or p-chlorobenzenesulphonyl, o-, m- or p-methoxy benzenesulphonyl, methanesulphonyl, dimethylaminosulphonyl, thienylsulphonyl, benzoyl, acetyl, furoyl and tert-butoxycarbonyl.

Suitable identities for R^5 include hydroxy, methoxy, ethoxy, propoxy, benzyloxy, nitrile, fluorine, chlorine and bromine. Preferably, there is no more than one R^5 substituent (i.e. p and q are 0 or 1), and when a single R^5 substituent is present, it is preferably in the para-position relative to the indole nitrogen.

In the compounds of Formula I, p is preferably zero; R^1 and R^2 are preferably identical and represent hydrogen or methyl; R^3 preferably represents hydrogen or benzoyl; and R^4 preferably represents arylsulphonyl or dimethylaminosulphonyl. Examples of specific compounds in accordance with Formula I include:

2-[1-(benzenesulphonyl)-1H-indol-4-yl]ethylamine;

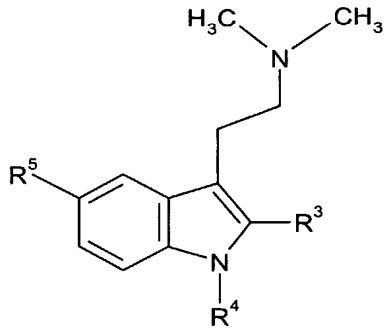
N,N-dimethyl 2-[1-(benzenesulphonyl)-1H-indol-4-yl]ethylamine;

N,N-dimethyl 3-[1-(benzenesulphonyl)-1H-indol-4-yl]propylamine; and

N,N-dimethyl 2-[1-(benzenesulphonyl)-2-benzoyl- 1H-indol-4-yl]ethylamine.

In the compounds of Formula II, preferably R^1 and R^2 are identical and represent hydrogen or methyl, or together complete a pyrrolidinyl, piperidinyl, piperazinyl or 4-methylpiperazinyl ring; R^3 preferably represents hydrogen or methyl; R^4 preferably represents arylsulphonyl, thienylsulphonyl, benzoyl or tert-butoxycarbonyl; R^5 preferably represents hydroxy, methoxy, benzyloxy or nitrile; and q is zero or 1.

A sub-class of compounds in accordance with Formula II is defined by Formula II(a):



(II(a))

where R^3, R^4 and R^5 have the same meanings as before.

Specific examples of compounds in accordance with Formula II(a) include:

N,N-dimethyl 2-[1-(benzenesulphonyl)-5-methoxy-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(4-methyl benzenesulphonyl)-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-[1-(4-chlorobenzenesulphonyl)-5-methoxy- 1H-indol-3yl]ethylamine;

N,N-dimethyl 2-[1-(3-chlorobenzenesulphonyl)-5-methoxy-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(2-naphthalenesulphonyl)-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(4-methoxybenzenesulphonyl)-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-[1-(2-chlorobenzenesulphonyl)-5-methoxy-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-(1-benzoyl-5-methoxy-1H-indol-3-yl)ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(2-thiophenesulphonyl)-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-[(1-benzenesulphonyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-(1-benzenesulphonyl-1H-indol-3-yl)ethylamine;

N,N-dimethyl 2-(1-methylsulphonyl-1H-indol-3-yl)ethylamine;

N,N-dimethyl 2-(5-methoxy-1-methylsulphonyl-1H-indol-3-yl)ethylamine;

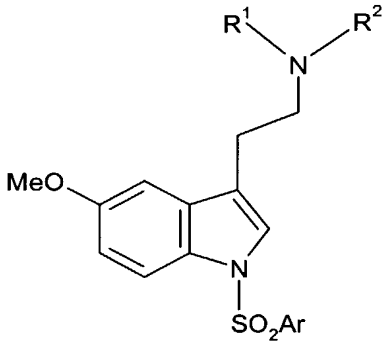
3-(2-dimethylamino-ethyl)-5-hydroxy-1H-indole-1-carboxylic acid tert-butyl ester;

N,N-dimethyl 2-[(1-benzenesulphonyl)-5-benzyloxy-1H-indol-3-yl)]ethylamine;

N,N-dimethyl 2-[(1-benzenesulphonyl)-5-hydroxy-1H-indol-3-yl)]ethylamine; and

N,N-dimethyl 2-[(1-benzenesulphonyl)-5-cyano-1H-indol-3-yl)]ethylamine.

A further sub-class of compounds in accordance with Formula II is defined by Formula II(b):



(II(b))

where R^1 and R^2 have the same meanings as before, and Ar represents an aryl or heteroaryl group.

Specific examples of compounds in accordance with Formula II(b) include:

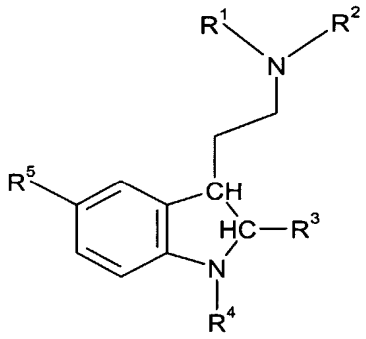
2-[1-(benzenesulphonyl)-5-methoxy-1H-indol-3-yl]ethylamine;

1-benzenesulphonyl-5-methoxy-3-[(2-pyrrolidin-1-yl)ethyl]-1H-indole;

1-benzenesulphonyl-5-methoxy-3-[(2-piperidin-1-yl)ethyl]-1H-indole; and

1-benzenesulphonyl-5-methoxy-3-[(2-piperazin-1-yl)ethyl]-1H-indole.

A third sub-class of compounds in accordance with Formula II is defined by Formula II(c):



(II(c))

where R^1 -R^5 have the same meanings as before.

Specific examples of compounds in accordance with Formula II(c) include:

N,N-dimethyl 2-(1-benzenesulphonyl-5-methoxy-2,3-dihydro-1H-indol-3-yl)ethylamine.

In the compounds of Formula III, R^1 and R^2 are preferably identical and represent hydrogen or methyl; R^3 preferably represents hydrogen; R^4 preferably represents arylsulphonyl, especially p-toluenesulphonyl; R^6 preferably represents hydroxy or methoxy; and p is preferably zero. Specific examples of compounds in accordance with Formula III include:

trans-4-dimethylamino-5-hydroxy-1-(4-methylbenzenesulphonyl)-1,3,4,5-tetrahydro-benz[*c,d*]indol-5-ol; and

trans-4-dimethylamino-5-methoxy-1-(4-methylbenzenesulphonyl)-1,3,4,5-tetrahydro-benz[*c,d*]indole.

The compounds of Formulae I–III, to be used according to the invention, can be prepared according to the methods described in US 6,187,805 and GB 2,341,549.

The present invention relates a method for the treatment or prophylaxis of obesity or for the reduction of food intake in mammals, including humans. The method comprises administering to a subject (e.g., a mammal, a human, a horse, a dog, or a cat) in need of such treatment a therapeutically effective amount of one or more compounds described above, or a composition having one or more compounds of formulae I-III in it.

The method delineated herein can also include the step of identifying that the subject is in need of treatment of the aforementioned diseases or conditions. The identification can be in the judgment of a subject or a health care professional and can be a subjective (e.g., opinion) or objective (e.g., measurable by a test or diagnostic method).

Further, the invention relates to the use of compounds of Formula I, II and II, as described herein, in the manufacture of a medicament for the treatment of obesity or for the reduction of food intake.

The invention also relates to the cosmetic use of compounds of Formula I, II and II, as described herein, for causing loss of weight, as well as cosmetic compositions containing said compounds. The invention further provides a non-therapeutic method of improving the bodily appearance of a mammal, including a human, which comprises orally administering to said mammal a compound of formula I, II or III as described herein.

"An effective amount" refers to an amount of a compound that confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). The dose level of the compounds described above, and the frequency of dosage of the specific combination, will vary depending on a variety of factors including the potency of each specific compound employed, the metabolic stability and length of action of that compound, the patient's age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the condition to be treated, and the patient undergoing therapy. The daily dosage may, for example, range from about 0.001 mg to about 150 mg per kilo of body weight, preferably from about 0.01 mg to about 100 mg per kilo of body weight, especially from about 0.1 to about 50 mg per kilo of body weight the compound of formula I, administered singly

or multiply in doses, e.g. dosages of from about 0.01 mg to about 25 mg each. Usually, such a combined dosage is given orally but e.g. parenteral or rectal administration may also be chosen. A currently preferred oral daily dosage for a human subject is from about 1 to about 80 mg, preferably from about 1 to about 50 mg per day.

The compounds discussed above can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of one, or optionally more, compound(s) discussed above in association with compatible pharmaceutically acceptable carrier materials, or diluents, as are well known in the art. The carriers may be any inert material, organic or inorganic, suitable for oral, enteral, rectal, percutaneous, subcutaneous or parenteral administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmacologically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavoring agents, buffers, and the like.

The compositions according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, pills, capsules, powders, syrups, elixirs, dispersible granules, cachets, suppositories and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, sprays, e.g. a nasal spray, transdermal preparations, e.g. patches, and the like.

The specific examples below are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. All publications cited herein are hereby incorporated by reference in their entirety.

Example

Effect on food intake of N,N-Dimethyl 2-[1-(benzenesulphonyl)-5-methoxy-1H-indol-3-yl]ethylamine by single dose subcutaneous administration in ob/ob mice.

Animals

Obese (ob/ob) mouse is selected as the primary animal model for screening as this mutant mouse consumes high amounts of food resulting in a high signal to noise ratio. To further substantiate and compare efficacy data, the effect of the compounds on food consumption is also studied in wild type (C57BL/6J) mice. The amount of food consumed during 15 hours of infusion of compounds is recorded.

Male mice (obese C57BL/6JBom-Lep^{ob} and lean wild-type C57B1/6JBom; Bomholtsgaard, Denmark) 8-9 weeks with an average body weight of 50 g (obese) and 25 g (lean) are used in all the studies. The animals are housed singly in cages at 23±1°C, 40-60 % humidity and have free access to water and standard laboratory chow. The 12/12-h light/dark cycle is set to lights off at 5 p.m. The animals are conditioned for at least one week before start of study.

Compound

The test compound, N,N-Dimethyl 2-[1-(benzenesulphonyl)-5-methoxy-1H-indol-3-yl]ethylamine, was dissolved in 25% polyethylene glycol 400 (PEG 400) plus 0,1% Tween 80 plus sodium acetate until pH 5. Doses of 30, 50 and 50 mg kg^{-1} were used. The purity of the test compounds is of analytical grade.

Animal dosage

Sex, Strain and Species:	Male C57BL/6J-Lep^{ob}/Lep^{ob} (ob/ob) mouse
Age & Weight:	approx 10 weeks (~ 45 gram)
Route:	sc
Dose (mg salt/kg):	10, 30, 50
Injection volume (ml)	0.25
Dose volume (ml/kg):	5
No of administrations	Single dose

Time of administration	4.30 pm (lights off 5 pm)
No. of animals/ treatment group:	8
Total no. of animals:	32

Experimental design

The animals were divided into four groups containing 8 animals each and treated with vehicle plus three dosages of the test compound. Food consumption, total motor activity and water consumption were measured continuously for 22 h following start of recording in a computer-assisted operant test cage system (Eater meter). The animals were habituated for two days. The third day was defined as the day before treatment (basal). On the fourth day the animals were treated with test compound just before dark onset (5 pm) and data recorded cumulatively for 3 h, 6 h, 12 h and 21 h. Water consumption during 22 h was also measured by weighing the days before and after treatment.

Statistical evaluation

Animals were randomized according to body weight and treatment assigned in a cage- and room-wise order. The food intake data are corrected for spillage during the test period of 22 h. Spillage at other time points were calculated proportionally to that of the 22 h spillage. The values are expressed as mean ± SEM both as the change in gram from basal level and as % of basal level. Statistical evaluation was performed on the percentage basal values using Kruskal-Wallis one-way ANOVA and, if significant, followed by Mann-Whitney U-test for test of significance between treatment groups. ID_{20} values (mg salt/kg) are estimated by visual inspection and indicates the dose causing 20% inhibition of response.

Results

N,N-Dimethyl 2-[1-(benzenesulphonyl)-5-methoxy-1H-indol-3-yl]ethylamine decreases food intake significantly at 6 h and 12 h following administration by

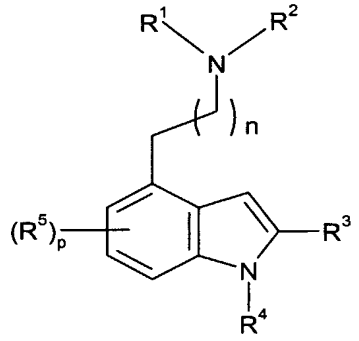
approximately 15-20 %, see Figure 1. This effect was not dose-dependent since all doses overlapped. Total activity was not affected.

Approximate minimum effective dose 10 mg/kg (borderline statistical significance of 15-20% inhibition) for food intake.

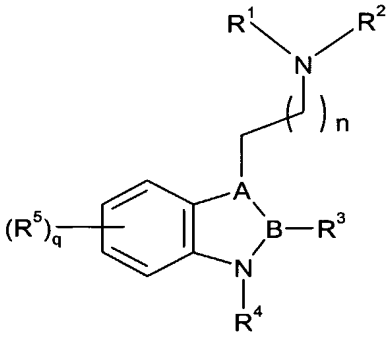
5

Claims

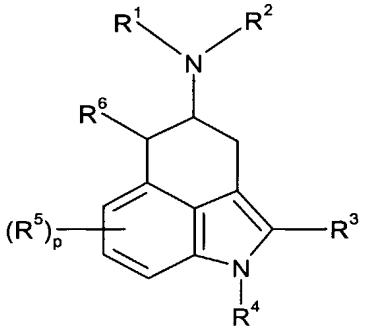
1. Use of a compound having a structure in accordance with Formula I, II or III:



(I)



(II)



(III)

wherein

n is 1 or 2;

p is 0,1,2 or 3;

q is 0,1,2,3 or 4;

R^1 and R^2 independently represent hydrogen, C_{1-6} alkyl or aryl (C_{1-6})alkyl, or together represent the atoms necessary to complete a heterocycloalkyl group comprising the nitrogen atom to which R^1 and R^2 are attached;

R^3 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl(C_{1-6})alkyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, C_{1-6} alkylcarbonyl, or (C_{1-6})alkoxycarbonyl;

R^4 represents arylsulphonyl, heteroarylsulphonyl, C_{1-6} alkylsulphonyl, di(C_{1-6})alkylaminosulphonyl, arylcarbonyl, C_{1-6} alkylcarbonyl, heteroarylcarbonyl or C_{1-6} alkoxycarbonyl;

each R^5 independently represents hydrogen, hydroxy, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy, nitrile or halogen;

R^6 represents hydrogen, hydroxy or C_{1-6} alkoxy; and

A–B represents C=C or CH–CH,

in the manufacture of a medicament for the treatment and/or prevention of obesity or for the reduction of food intake.

2. Use according to claim 1 in which said compound is in accordance with said Formula I or II or III wherein:

R^1 and R^2 independently represent hydrogen, methyl, ethyl, propyl or benzyl, or R^1 and R^2 in combination represents pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl or morpholinyl;

R^3 represents hydrogen, methyl, ethyl, benzyl, allyl, propargyl, benzoyl, phenyl, thienyl, furoyl, or ethoxycarbonyl;

R^4 represents benzenesulphonyl, 2-naphthalenesulphonyl, o-, m- or p-toluenesulphonyl, o-, m- or p-chlorobenzenesulphonyl, o-, m- or p-

methoxybenzenesulphonyl, methanesulphonyl, dimethylaminosulphonyl, thienylsulphonyl, benzoyl, acetyl, furoyl or tert-butoxycarbonyl; and

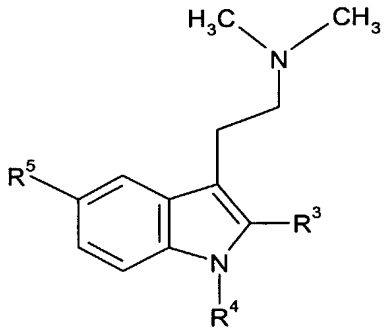
R^5 represents hydrogen, hydroxy, methoxy, ethoxy, propoxy, benzyloxy, nitrile, fluorine, chlorine or bromine.

3. Use according to claim 1or 2 in which the compound is selected from:
(a) compounds of Formula I in which p is zero; R^1 and R^2 are identical and represent hydrogen or methyl; R^3 represents hydrogen or benzoyl; R^4 represents arylsulphonyl or heteroarylsulphonyl; and R^5 represent hydrogen or methoxy; and
(b) compounds of Formula II in which R^1 and R^2 are identical and represent hydrogen or methyl, or together complete a pyrrolidinyl, piperidinyl, piperazinyl or 4-methylpiperazinyl ring; R^3 represents hydrogen or methyl; R^4 represents arylsulphonyl, thienylsulphonyl, benzoyl or tert-butoxycarbonyl; R^5 represents, hydroxy, methoxy, benzyloxy or nitrile; and q is zero or 1.
(c) compounds of Formula III in which R^1 and R^2 are identical and represent hydrogen or methyl; R^3 represents hydrogen; R^4 represents arylsulphonyl; R^6 represents hydrogen, hydroxy or methoxy; and p is zero.

4. Use according to any one of claims 1 to 3 in which the compound is in accordance with Formula I.

5. Use according to claim 4, wherein the compound is:
2-[1-(benzenesulphonyl)-1H-indol-4-yl]ethylamine;
N,N-dimethyl 2-[1-(benzenesulphonyl)-1H-indol-4-yl]ethylamine;
N,N-dimethyl 3-[1-(benzenesulphonyl)-1H-indol-4-yl]propylamine; or
N,N-dimethyl 2-[1-(benzenesulphonyl)-2-benzoyl- 1H-indol-4-yl]ethylamine.

6. Use according to any one of claims 1 to 3 in which the compound is in accordance with Formula II(a):



II (a),

wherein R^3, R^4, and R^5 are as defined in claim 1.

7. Use according to claim 6 in which the compound is:

N,N-dimethyl 2-[1-(benzenesulphonyl)-5-methoxy-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(4-methyl benzenesulphonyl)-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-[1-(4-chlorobenzenesulphonyl)-5-methoxy- 1H-indol-3yl]ethylamine;

N,N-dimethyl 2-[1-(3-chlorobenzenesulphonyl)-5-methoxy-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(2-naphthalenesulphonyl)-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(4-methoxybenzenesulphonyl)-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-[1-(2-chlorobenzenesulphonyl)-5-methoxy-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-(1-benzoyl-5-methoxy-1H-indol-3-yl)ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(2-thiophenesulphonyl)-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-[(1-benzenesulphonyl)-5-methoxy-2-methyl-1H-indol-3-yl]ethylamine;

N,N-dimethyl 2-(1-benzenesulphonyl-1H-indol-3-yl)ethylamine;

N,N-dimethyl 2-(1-methylsulphonyl-1H-indol-3-yl)ethylamine;

N,N-dimethyl 2-(5-methoxy-1-methylsulphonyl-1H-indol-3-yl)ethylamine;

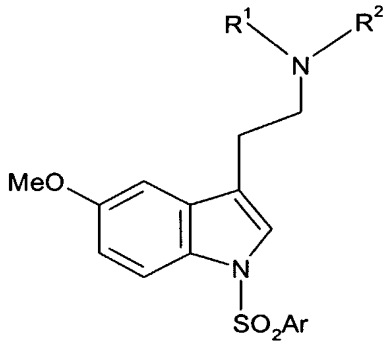
3-(2-dimethylamino-ethyl)-5-hydroxy-1H-indole-1-carboxylic acid tert-butyl ester;

N,N-dimethyl 2-[(1-benzenesulphonyl)-5-benzyloxy-1H-indol-3-yl)]ethylamine;

N,N-dimethyl 2-[(1-benzenesulphonyl)-5-hydroxy-1H-indol-3-yl)]ethylamine; or

N,N-dimethyl 2-[(1-benzenesulphonyl)-5-cyano-1H-indol-3-yl)]ethylamine.

8. Use according to any one of claims 1 to 3 in which the compound is in accordance with formula II(b):



(II(b))

wherein R^1 and R^2 are as defined in claim 1, and Ar represents an aryl or heteroaryl group.

9. Use according to claim 8, wherein R^1 and R^2 are methyl groups.

10. Use according to any one of claim 8 or 9, wherein Ar is selected from the group consisting of phenyl, 2-thienyl, and 3-chlorophenyl.

11. Use according to claim 8, wherein the compound is:

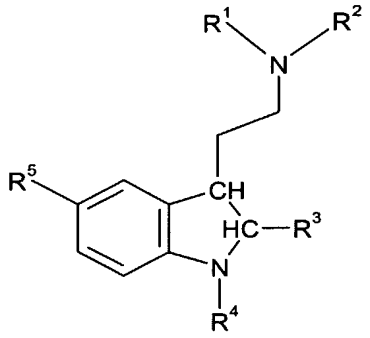
2-[1-(benzenesulphonyl)-5-methoxy-1H-indol-3-yl]ethylamine;

1-benzenesulphonyl-5-methoxy-3-[(2-pyrrolidin-1-yl)ethyl]-1H-indole;

1-benzenesulphonyl-5-methoxy-3-[(2-piperidin-1-yl)ethyl]-1H-indole; or

1-benzenesulphonyl-5-methoxy-3-[(2-piperazin-1-yl)ethyl]-1H-indole.

12. Use according to any one of claims 1 to 3 in which the compound is in accordance with Formula II(c):



II(c),

wherein R^1, R^2, R^3, R^4, and R^5 are as defined in claim 1.

13. Use according to claim 12, wherein the said compound is N,N-dimethyl-2-[1-(benzenesulphonyl)-5-methoxy-1H-indol-3-yl]ethylamine.

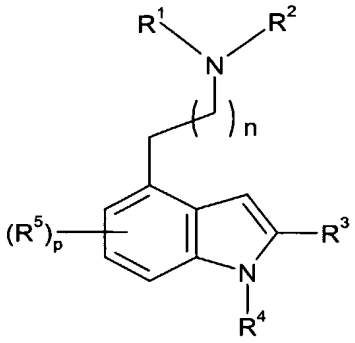
14. Use according to any one of claims 1 to 3 in which the compound is in accordance with Formula III.

15. Use according to claim 14, wherein the compound is

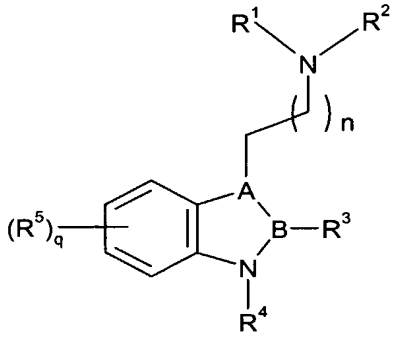
trans-4-dimethylamino-5-hydroxy-1-(4-methylbenzenesulphonyl)-1,3,4,5-tetrahydro-benz[*c,d*]indol-5-ol; or

trans-4-dimethylamino-5-methoxy-1-(4-methylbenzenesulphonyl)-1,3,4,5-tetrahydro-benz[*c,d*]indole.

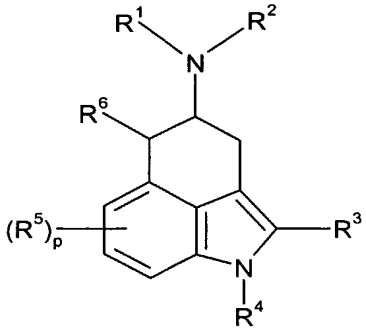
16. A method for the treatment and/or prevention of obesity or for the reduction of food intake, comprising administering to a patient in need of such treatment an effective amount of a compound, or a pharmaceutically acceptable salt or prodrug thereof, having a structure in accordance with Formula I, II or III:



(I)



(II)



(III)

wherein

n is 1 or 2;

p is 0,1,2 or 3;

q is 0,1,2,3 or 4;

R^1 and R^2 independently represent hydrogen, C_{1-6} alkyl or aryl (C_{1-6})alkyl, or together represent the atoms necessary to complete a heterocycloalkyl group comprising the nitrogen atom to which R^1 and R^2 are attached;

R^3 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl(C_{1-6})alkyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, C_{1-6} alkylcarbonyl, or (C_{1-6})alkoxycarbonyl;

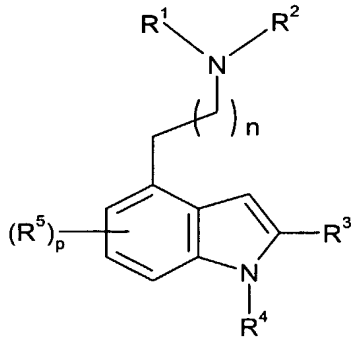
R^4 represents arylsulphonyl, heteroarylsulphonyl, C1-6 alkylsulphonyl, di(C_{1-6})alkylaminosulphonyl, arylcarbonyl, C_{1-6} alkylcarbonyl, heteroarylcarbonyl or C_{1-6} alkoxycarbonyl;

each R^5 independently represents hydrogen, hydroxy, C_{1-6} alkoxy, aryl(C_{1-6}) alkoxy, nitrile or halogen;

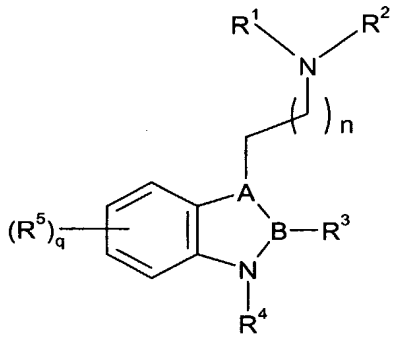
R^6 represents hydrogen, hydroxy or C_{1-6} alkoxy; and

A–B represents C=C or CH–CH.

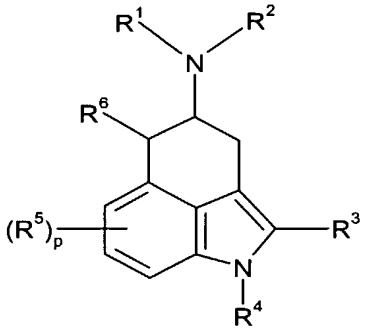
17. Use as a cosmetic product of a compound having a structure in accordance with Formula I, II or III:



(I)



(II)



(III)

wherein

n is 1 or 2;

p is 0,1,2 or 3;

q is 0,1,2,3 or 4;

R^1 and R^2 independently represent hydrogen, C_{1-6} alkyl or aryl (C_{1-6})alkyl, or together represent the atoms necessary to complete a heterocycloalkyl group comprising the nitrogen atom to which R^1 and R^2 are attached;

R^3 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl(C_{1-6})alkyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, C_{1-6} alkylcarbonyl, or (C_{1-6})alkoxycarbonyl;

R^4 represents arylsulphonyl, heteroarylsulphonyl, C_{1-6} alkylsulphonyl, di(C_{1-6})alkylaminosulphonyl, arylcarbonyl, C_{1-6} alkylcarbonyl, heteroarylcarbonyl or C_{1-6} alkoxycarbonyl;

each R^5 independently represents hydrogen, hydroxy, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy, nitrile or halogen;

R^6 represents hydrogen, hydroxy or C_{1-6} alkoxy; and

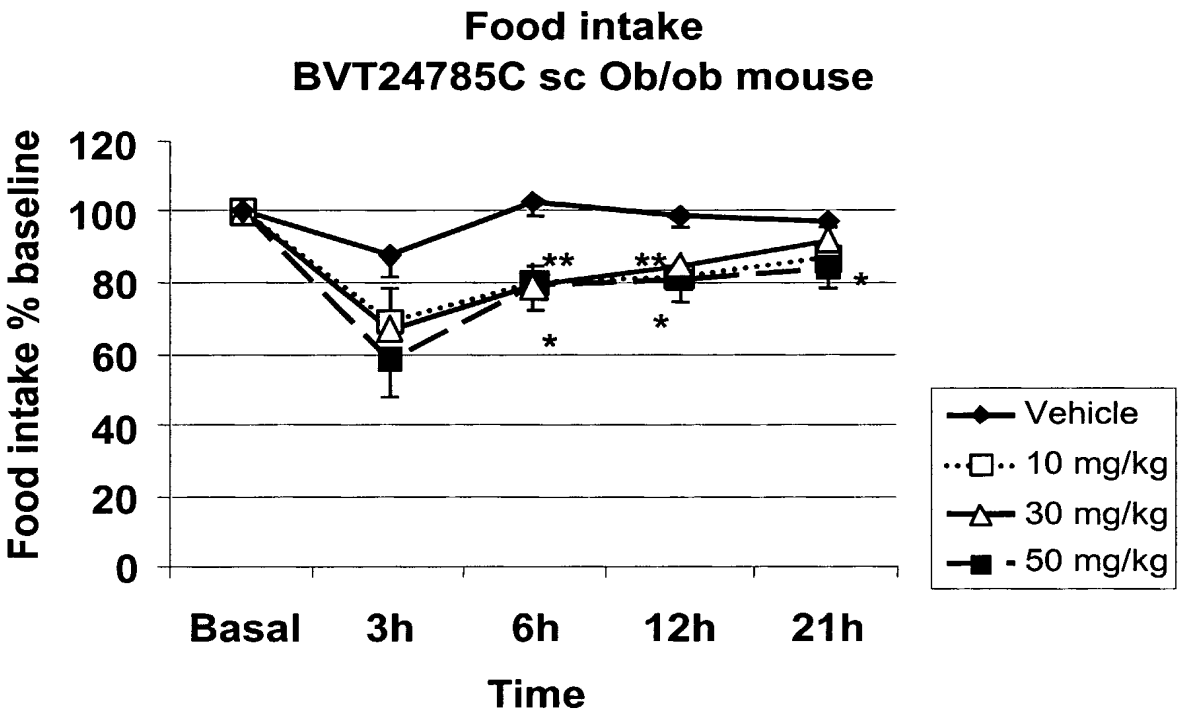
A–B represents C=C or CH–CH,

for causing loss of weight.

18. Cosmetic compositions, characterized in that they contain a compound as defined in claim 17.

19. A non-therapeutic method of improving the bodily appearance of a mammal, which comprises orally administering to said mammal a compound as defined in claim 17, or a pharmaceutically effective salt thereof, in a dosage effective to reduce appetite, and repeating said dosage until a cosmetically beneficial loss of body weight has occurred.

Figure 1


Food intake
BVT24785C sc Ob/ob mouse
Food intake % baseline
120
100
80
60
40
20
0
Basal
3h
6h
12h
21h
Time
Vehicle
10 mg/kg
30 mg/kg
50 mg/kg

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01929

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/4045, A61P 3/04 // C07D 209/04, C07D 209/90, C07D 403/12, C07D 409/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA, EMBASE, MEDLINE, BIOSIS, EPO-INTERNAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0375133 A1 (THE UPJOHN COMPANY), 27 June 1990 (27.06.90), page 41, line 13 - line 19, and claims --	1-9
X	WO 9207829 A1 (THE UPJOHN COMPANY), 14 May 1992 (14.05.92), see the claims --	1-19
X	US 4576959 A (FLAUGH), 18 March 1986 (18.03.86), column 3, line 21, and claims --	1-19
Y	GB 2341549 A (MERCK SHARP & DOHME LIMITED), 22 March 2000 (22.03.00) --	1-19

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 February 2003	07 -02- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer NEBIL GECER/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01929

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	British Journal of Pharmacology, Volume 126, 1999, Suppl., 66P, J.C. Bentley et al: "Effect of the 5-HT6 antagonist, Ro 04-6790 on food consumption in rats trained to a fixed feeding regime"	1-19
	--	
A	Obesity Research, Volume 3, suppl. 4, Nov, 1995, Colin T. Dourish: "Multiple Serotonin Receptors: Opportunities for New Treatment for Obesity", pages 449S-461S	1-19
	--	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/01929

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claim 16 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/12/02

International application No.
PCT/SE 02/01929

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0375133 A1	27/06/90	AU 4649189 A	12/06/90
		CA 2002415 A	14/05/90
		IL 92294 D	00/00/00
		JP 4501722 T	26/03/92
		US 5245046 A	14/09/93
		WO 9005721 A	31/05/90
WO 9207829 A1	14/05/92	AU 8876591 A	26/05/92
US 4576959 A	18/03/86	AT 53021 T	15/06/90
		AU 572258 B	05/05/88
		AU 3841985 A	15/08/85
		CA 1291484 A	29/10/91
		CY 1657 A	14/05/93
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		DK 48785 A	03/09/85
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		ES 540151 A	16/03/86
		ES 548942 A	16/04/87
		ES 8605236 A	16/08/86
		ES 8704894 A	01/07/87
		GR 850313 A	05/06/85
		HK 63792 A	28/08/92
		HU 37121 A	28/11/85
		HU 193941 B	28/12/87
		IE 57916 B	19/05/93
		IE 850263 L	06/08/85
		IL 74222 A	31/07/88
		JP 1970327 C	18/09/95
		JP 2027267 C	26/02/96
		JP 6099388 B	07/12/94
		JP 6279406 A	04/10/94
		JP 7045470 B	17/05/95
		JP 60208959 A	21/10/85
		KR 8601892 B	24/10/86
		MX 9203124 A	01/07/92
		NZ 211031 A	29/08/89
		PH 20490 A	21/01/87
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		SU 1375128 A	15/02/88
		US 4983622 A	08/01/91
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		ZA 8500916 A	24/09/86
GB 2341549 A	22/03/00	GB 9820113 D	00/00/00
		GB 9921054 D	00/00/00
		US 6187805 B	13/02/01